REMARKS/ARGUMENTS

The Pending Claims

Claims 1, 3, 4, and 13 are currently pending and are directed to a method for the therapeutic treatment of a carcinoma in a mammal.

The Office Action

The Office Action rejects claims 1, 3, 4, and 13 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement and written description. Reconsideration of these rejections is hereby requested.

Discussion of Enablement Rejection

The Office Action has rejected claims 1, 3, 4, and 13 under Section 112, first paragraph, as allegedly lacking enablement. This rejection is traversed for the reasons set forth below.

Specifically, the Office Action contends that the specification does not enable the use of *any* inhibitor of a mutated FGFR-4 protein according to the method of claim 1. Moreover, because the specification allegedly does not disclose a mechanism by which a point mutation in the transmembrane domain of FGFR-4 renders the receptor constitutively active, one of ordinary skill in the art would not be able to determine what type of molecule could function as an FGFR-4 inhibitor without undue experimentation.

Contrary to the assertion of the Office Action, the mechanism by which the FGFR-4 is activated is disclosed in the instant application as including (1) ligand binding, (2) dimerization, (3) trans-phosphorylation, and (4) activation (see paragraphs 0034-0038). Moreover, the instant application also discloses that the mutation that results in the claimed amino acid substitution at position 388 of SEQ ID NO: 9 activates the FGFR-4 by increasing dimerization of the receptor without ligand binding, which leads to transphosphorylation and activation of the mutated FGFR-4. Thus, because the specification clearly discloses that activation of the mutated FGFR-4 is mediated via the kinase domain of the protein, one of ordinary skill in the art would recognize that any RTK inhibitor known in the art can be used to inhibit a mutated FGFR-4 as presently claimed.

Receptor tyrosine kinase (RTK) inhibitors that can be used in connection with the claimed invention were known in the art at the time the instant application was filed. For example, specific RTK inhibitors are disclosed in Mohammadi et al., *Science*, *276*: 955-960 (1997), which is referred to in the specification (see 0047). In addition, Dahring et al., *J. Pharmacol. Exp. Ther.*, *281*: 1446-1456 (1997), discloses a 6-arylpyrido[2,3]pyrimidine, which blocks bFGF-induced DNA synthesis and mitogenesis as well as EGFR and PDGFR activity. Hamby et al., *J. Med. Chem.*, *40*: 2296-2303 (1997), discloses a screening protocol to identify more selective 6-arylpyrido[2,3]pyrimidine-based compounds. Panek et al., *J. Pharmacol. Exp. Ther.*, *283*: 1433-1444 (1997), discloses a nanomolar inhibitor that blocks PDGF and EGF-stimulated receptor autophosphorylation in vascular smooth muscle cells and A431 cells, respectively, and blocks bFGF-mediated tyrosine phosphorylation in Sf9 cells. Batley et al., *Life Sciences*, *62*: 143-150 (1998), discloses an inhibitor (PD161570) which suppresses constitutive FGFR1 phosphorylation and exhibits 5-1000-fold higher affinity to FGFR as compared to PDGFR and EGFR. Small molecule inhibitors of PDGF and FGFR family members are disclosed in Showalter et al., *Pharmacol. Ther.*, *76*: 55-71 (1997).

Furthermore, receptor tyrosine kinase (RTK) inhibitors that can be used in connection with the claimed invention are disclosed in the instant application. In this regard, the specification discloses specific inhibitors to be used in the method of claim 1, such as a low-molecular weight substance directed against an RTK, a kinase-inactive receptor, and an anti-receptor antibody (paragraph 0017). With respect to kinase-inactive receptors, the specification discloses that a kinase-inactive receptor inhibits the activity of RTKs by forming heterodimers, thereby creating a dilution effect because the heterodimers are not capable of signal transfer (see paragraph 0042). Moreover, the functional regions of RTKs, including FGFR-4, were known in the art at the time the instant application was filed. Using this knowledge, one of ordinary skill in the art could have easily produced a kinase-inactive FGFR-4 receptor using only routine experimentation, which is further evidenced by the Ezzat reference cited in the Office Action. Other examples of kinase-inactive receptors are disclosed in Li et al., *MCB*, *14*: 7660-7669 (1992), Ueno et al., *J. Biol. Chem.*, *267*: 1470-1476 (1992), and Hardcastle et al., *Curr. Biol.*, *10*: 1511-1514 (2002) ("the Hardcastle reference"). Indeed, the Hardcastle reference discloses the efficiency of a truncated FGFR-4 *in vivo* (see page 1513, Figure 3).

With respect to anti-receptor antibody inhibitors, methods for making such antibodies were known in the art at the time of the filing of the instant application (see, e.g., Hudziak et al., *Mol. Cell. Biol.*, *9*: 1165-1172 (1989)). Antibodies that are specifically immunoreactive with mutated isoforms of proteins also were described in the art at the time of the filing of the instant application (see, e.g., WO 96/36641, WO 96/31605, and WO 95/21938). Thus, based on the knowledge in the prior art, one of ordinary skill in the art could generate anti-FGFR-4 antibodies using only routine experimentation.

Accordingly, using the guidance provided by the specification and the knowledge in the art at the time the instant application was filed, one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation. Therefore, the enablement rejection under Section 112, first paragraph, is improper and should be withdrawn.

Discussion of Written Description Rejection

The Office Action has rejected claims 1, 3, 4, and 13 under Section 112, first paragraph, as allegedly lacking written description. This rejection is traversed for the reasons set forth below.

Confusingly, the Office Action alleges that the specification does not disclose a single species of the genus of FGFR-4 inhibitors, but rather "discloses such species as small molecules, antibodies, and kinase-inactive receptors" (Office Action at page 6, third complete paragraph).

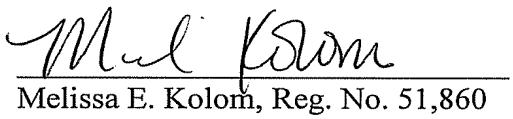
Contrary to the assertion of the Office Action, one of ordinary skill in the art would understand that Applicants had possession of the invention of claim 1 because the specification discloses a representative number of species of FGFR-4 inhibitors. In this regard, and as discussed above, the specification discloses specific inhibitors to be used in the method of claim 1, such as a low-molecular weight substance directed against an RTK, a kinase-inactive receptor, and an anti-receptor antibody (specification at, e.g., page 4, paragraph 0017). As indicated above with respect to the enablement rejection, such inhibitors also were known in the art at the time the subject application was filed (e.g., as disclosed in Mohammadi et al., *supra*).

Accordingly, the subject matter of claim 1, as well as the claims depending therefrom, is described in the specification so as to reasonably convey to one of ordinary skill in the art the inventors had possession of the claimed invention. Thus, the written description under Section 112, first paragraph, is improper and should be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



Melissa E. Kolom, Reg. No. 51,860
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6731
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: September 21, 2007